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03 MAY 2001

Attny Docket No. C1190/20008  
PTO CUSTOMER NO. 03000

**TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371**

(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

International Application No. : PCT/FR99/02681  
International Filing Date : November 3, 1999  
Priority Date Claimed : FR 98/14034  
Filed on November 6, 1998  
Title of Invention : IMPROVED FAST DISINTEGRATING TABLET  
Applicant(s) for DO/EO/US : Charles CHAUVEAU  
Jean-Marc ZUCCARELLI  
Nourredine NOURI  
Maryvonne BARBERO

Box PCT  
Commissioner of Patents and Trademarks  
Washington, D.C. 20231

Attention: EO/US

Sir:

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).

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3. A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
4. A copy of the International Application as filed (35 U.S.C 371(c)(2)) has been transmitted by the International Bureau. A copy of the cover sheet of international application as published on May 18, 2000, under International Publication No. WO 00/27357 is enclosed.
5. An English translation of International Application No. PCT/FR99/02682 is enclosed.
6. A FIRST preliminary amendment is enclosed.
7. An Abstract is attached to the preliminary amendment.

The Declaration and Assignment will follow at a later date.

8. The following fees are submitted:

**BASIC NATIONAL FEE (37 CFR 1.492(1)(1)-(5):**

Claims Fee	For	Number Filed	Number Extra	Rate	Calculation
	Total Claims	12	0	x 18	\$
	Independent Claims	1	0	x 80	
	Multiple Dependent Claims			x270	
<b>Basic Fee</b>	U.S. PTO was not International Preliminary Examination Authority. Search report on the international application was prepared by the European Patent Office				\$ 860
	Total of above Calculations				\$ 860
	Reduction by 1/2 for filing by small entity				
	Subtotal				\$
	<b>TOTAL NATIONAL FEE</b>				<b>\$ 860</b>

Please charge counsel's account no. 03-0075 in the amount of \$860, or any additional amount which may be required, to cover the above fees. A duplicate copy of the calculation sheet is enclosed.

**AUTHORIZATION TO CHARGE ADDITIONAL FEES**

The Commissioner is hereby authorized to charge the following additional fees which may be required by this paper and during the entire pendency of this application to counsel's deposit account no. 03-0075:

1. 37 CFR 1.492(a)(1), (2), (3) and (4) (filing fees)
2. 37 CFR 1.492(b), (c) and (d) (presentation of extra claims)
3. 37 CFR 1.17 (application processing fees)
4. 37 CFR 1.492(e) and (f) (surcharge fee for filing declaration and/or filing an English translation of an International Application later than 30 months after the priority date)

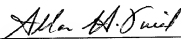
This application and items attached are being transmitted before the 30 month claimed priority date.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,  
COHEN & POKOTILOW, LTD.

May 3, 2001

By



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PATENT

Attorney Docket: C1190/20008

PTO CUSTOMER NUMBER: 03000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
PATENT EXAMINING OPERATION

Applicants : Charles CHAUVEAU, Jean-Marc ZUCCARELLI  
Nourredine NOURI and Maryvonne BARBERO

Serial No. : U.S. National Phase of PCT/FR99/02681  
filed November 3, 1999

U.S. Filing Date: May 3, 2001

For : IMPROVED RAPIDLY DISINTEGRATING TABLET

**PRELIMINARY AMENDMENT**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

**IN THE CLAIMS:**

Cancel Claims 1-8, without prejudice, and add the following new claims:

-- 9. Improved multiparticulate tablet which disintegrates in contact with the saliva in the mouth in less than 40 seconds, wherein it is based on particles of coated active principle which have intrinsic compression characteristics, and on a mixture of excipients, the ratio of excipient mixture to coated active principle particles being 0.4 to 6 parts by weight, the mixture of excipients comprising: a disintegration agent; a soluble diluent agent with binding properties which consists of a polyol having less than 13 carbon atoms and being either in the form of the directly compressible product with an average particle

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10. Tablet according to Claim 9, wherein the ratio of excipient mixture to coated active principle particles is 1 to 4 parts by weight.

11. Tablet according to Claim 9, wherein the ratio of directly compressible polyol to powder polyol is 80/20 to 20/80.

12. Tablet according to Claim 9, wherein the proportion of disintegration agent is 2 to 7% by weight and the proportion of soluble agent is 40 to 70% based in each case on the weight of the tablet.

13. Tablet according to Claim 9, wherein the active principle is selected from the group consisting of aspirin, paracetamol and ibuprofen.

14. Tablet according to Claim 9, wherein the disintegrating agent is selected from the group consisting of croscarmellose, crospovidone and mixtures thereof.

15. Tablet according to Claim 9, wherein the permeabilizing agent is selected from the group consisting of silicas with a high affinity for aqueous solvents, such as precipitated silica, maltodextrins,  $\beta$ -cyclodextrins and mixtures thereof.

16. Tablet according to Claim 9, wherein the permeabilizing agent is precipitated silica.

17. Tablet according to Claim 9, wherein the proportion of permeabilizing agent is 0.1 to 10% based on the weight of the tablet.

18. Tablet according to claim 17, wherein the proportion of permeabilizing agent is 0.5 to 5% based on the weight of the tablet.

19. Tablet according to Claim 9, wherein the lubricant is selected from the group consisting of magnesium stearate, sodium stearyl fumarate, stearic acid, micronized polyoxyethylene glycol and mixtures thereof.

20. Tablet according to Claim 9, wherein the sweetener is selected from the group consisting of aspartame, potassium acesulfame, sodium saccharinate, neohesperidin dihydrochalcone and mixtures thereof. --

REMARKS

Claims 1-8 have been replaced by Claims 9-20 to eliminate multiple dependency included in the originally filed claims, and to conform the claims with U.S. practice.

The Abstract of the Disclosure is also attached hereto to comply with the requirements of 37 C.F.R. §1.72(b).

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,  
COHEN & POKOTILOW, LTD.

May 3, 2001

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**ABSTRACT**

The invention concerns an improved multiparticulate tablet disintegrating in the mouth in contact with saliva in less than 40 seconds. The invention is characterized in that it is based on particles of coated active principle, said particles having intrinsic compression properties and a mixture of carriers, the proportion of carrier mixture relative to coated active principle particles being 0.4 to 6 parts by weight, the carrier mixture comprising: a disintegrating agent; a diluting soluble agent with binding properties; a lubricant; a permeabilizing agent; and advantageously lubricants, sweeteners, flavoring and coloring agents, the proportion of disintegrating agent and soluble agent relative to the tablet mass being 1 to 15% by weight for the former and 30 to 90% by weight for the latter.

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## DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITE DE COOPERATION EN MATIERE DE BREVETS (PCT)

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(54) Title: IMPROVED FAST DISINTEGRATING TABLET			
(54) Titre: COMPRIME A DELITEMENT RAPIDE PERFECTIONNE			
(57) Abstract			
<p>The invention concerns an improved multiparticulate tablet disintegrating in the mouth in contact with saliva in less than 40 seconds. The invention is characterised in that it is based on particles of coated active principle, said particles having intrinsic compression properties and a mixture of carriers, the proportion of carrier mixture relative to coated active principle particles being 0.4 to 6 parts by weight, the carrier mixture comprising: a disintegrating agent; a diluting soluble agent with binding properties; a lubricant; a permeabilizing agent; and advantageously lubricants, sweeteners, flavouring and colouring agents, the proportion of disintegrating agent and soluble agent relative to the tablet mass being 1 to 15 wt.% for the former and 30 to 90 wt.% for the latter.</p>			
(57) Abrégé			
<p>La présente invention a pour objet un comprimé multiparticulaire perfectionné se désagrégeant dans la bouche au contact de la salive en moins de 40 secondes, caractérisé par le fait qu'il est à base de particules de principe actif enrobé, lesdites particules présentant des caractéristiques intrinsèques de compression et d'un mélange d'excipients, la proportion de mélange d'excipients par rapport aux particules de principe actif enrobé étant de 0,4 à 6 parties en poids le mélange d'excipients comprenant un agent de désagréation, un agent soluble diluant à propriétés liantes, un lubrifiant, un agent perméabilisant, et, avantageusement des lubrifiants, des édulcorants, des arômes et des colorants, la proportion d'agent de désintégration et d'agent soluble par rapport à la masse du comprimé étant de 1 à 15 % en poids pour le premier et de 30 à 90 % en poids pour le second.</p>			

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**IMPROVED RAPIDLY DISINTEGRATABLE TABLET**

The invention relates to a rapidly disintegratable tablet of the type which disintegrates in the mouth in less than 40 seconds, said tablet comprising particles of coated active principle which have intrinsic compression characteristics, and a mixture of excipients.

Ibuprofen, paracetamol and aspirin may be mentioned as examples of active principles which can be used to produce the tablets according to the invention.

Tablets based on ibuprofen are already known.

Thus patent US 5,215,755 describes chewing tablets in which the ibuprofen is present in the form of granules having a coating based on hydroxyethyl cellulose or a hydroxyethyl cellulose/hydroxypropyl methyl cellulose mixture. This coating was chosen to overcome the observed deficiencies of the coatings of the prior art based on ethyl cellulose only.

The object of the invention is to provide tablets obtained with the aid of particles of coated active principle which not only disintegrate rapidly in the mouth in less than 40 seconds, but also have a pleasant palatability, together with satisfactory hardness characteristics enabling them to be manufactured industrially, and which keep sufficiently well under normal storage conditions to enable them to be handled by the patient, these tablets also optimizing the bioavailability of the active principle.

The tablet according to the invention is characterized in that it is based on particles of coated active principle which have intrinsic compression characteristics, and on a mixture of excipients, the ratio of excipient mixture to coated active principle being 0.4 to 6 parts by weight, preferably 1 to 4 parts by weight, the mixture of excipients comprising:

- a disintegration agent;
- a soluble diluent agent with binding properties which consists of a polyol having less than 13 carbon atoms and being either in the form of the directly compressible product with an average particle diameter of 100 to 500  $\mu\text{m}$ , or in the form of a powder with an average particle diameter of less than 100  $\mu\text{m}$ , this polyol preferably being selected from the group comprising mannitol, xylitol, sorbitol and maltitol, it being understood that sorbitol cannot be used alone and that, in the case where there is only one soluble diluent agent with binding properties, it is used in

the form of the directly compressible product, whereas in the case where there are at least two soluble diluent agents with binding properties, one is present in the directly compressible form and the other is present in powder form, it then being possible for the polyols to be the same, the ratio of directly compressible polyol to powder polyol being 99/1 to 20/80, preferably 80/20 to 20/80;

- a lubricant;
- a permeabilizing agent; and
- advantageously sweeteners, flavourings and colours,

the proportion of disintegrating agent being 1 to 15% by weight, preferably 2 to 7% by weight, and the proportion of soluble agent being 30 to 90% by weight, preferably 40 to 70% by weight, based in each case on the weight of the tablet.

The soluble diluent agent with binding properties consists of a polyol having less than 13 carbon atoms and being either in the form of the directly compressible product with an average particle diameter of between 100 and 500 micrometres, or in the form of a powder with an average particle diameter of less than 100 micrometres, this polyol preferably being selected from the group comprising mannitol, xylitol, sorbitol and maltitol, it being impossible to use sorbitol alone.

If there is a single soluble diluent agent with binding properties, therefore different from sorbitol, it is used in the form of the directly compressible product.

If at least two soluble diluent agents with binding properties are used, one is present in the form of the directly compressible product and the other, which can consist of the same polyol, is present in the form of a powder in which the average diameter of the constituent particles is less than 100 micrometres, the ratio of directly compressible polyol to powder polyol being 99/1 to 20/80, preferably 80/20 to 20/80.

The disintegration agent is selected from the group comprising especially crosslinked sodium carboxymethyl cellulose (known in the profession as croscarmellose), crospovidone and mixtures thereof. By virtue of the choice and proportion of this disintegration agent, the tablet retains an acceptable hardness for normal handling conditions when tablets are kept in leaktight packaging up to temperatures of at least 30°C.

The chosen proportions of disintegration agent and soluble agent for constituting the excipient are 1 to 15% by weight and 30 to 90% by weight, respectively, based in each case on the weight of the tablet.

The lubricant preferably used in this mixture of excipients is selected from the group comprising magnesium stearate, sodium stearyl fumarate, stearic acid, micronized polyoxyethylene glycol (micronized Macrogol 6000) and mixtures thereof. It can be used in a proportion of 0.05 to 2%, based on the total weight of the tablet.

The permeabilizing agent used is a compound selected from the group comprising especially silicas with a high affinity for aqueous solvents, such as the precipitated silica better known by the trade mark Syloid®, maltodextrins,  $\beta$ -cyclodextrins and mixtures thereof.

The permeabilizing agent allows the creation of a hydrophilic network which facilitates the penetration of the saliva and hence assists the disintegration of the tablet.

In one highly advantageous embodiment of the tablets according to the invention, the permeabilizing agent is the precipitated silica better known by the trade mark Syloid® FP244. In fact, this silica not only assists the disintegration of the tablets, but also, through its properties as a flow promoter, favours the rearrangements of the particles during compression, and it makes it possible on the one hand to reduce the amount of hydrophobic lubricant needed to ensure optimum manufacturing conditions, and on the other hand to reduce the intensity of the compression force needed to produce a tablet which can be handled under these industrial conditions.

The proportion of permeabilizing agent is between 0.5 and 5% by weight, based on the weight of the tablet.

A sweetener and optionally a flavouring and a colour are also included in the mixture of excipients forming part of the composition of the tablets according to the invention.

The sweetener can be selected from the group comprising especially aspartame, potassium acesulfame, sodium saccharinate, neohesperidin dihydrochalcone and mixtures thereof.

The flavourings and colours are those conventionally used in pharmacy for the preparation of tablets.

Compared with the already existing tablets of the type in question, the tablets according to the invention have an improved palatability and particularly an improved taste and texture, and can allow a reduction in the ratio of tablet weight

to active principle dose.

They have a satisfactory hardness, enabling them to be handled under standard operating conditions without special operating precautions. By way of indication, it is pointed out that hardnesses which satisfy these conditions are generally between 20 and 70 Newtons.

The tablets according to the invention can be prepared in the following manner or by any other appropriate process. Particles of coated active principle which have intrinsic compression characteristics are added to a mixture of excipients containing a disintegration agent, a soluble diluent agent with binding properties, a permeabilizing agent and advantageously a lubricant, sweeteners, flavourings and colours, in the proportions indicated above. The mixture obtained in this way is homogenized in a dry mixer and then subjected to a compression force which gives the resulting tablet a satisfactory hardness, enabling it to be manufactured industrially and handled under normal conditions without special operating precautions; by way of indication, it is pointed out that hardnesses which satisfy these conditions are generally between 20 and 70 Newtons.

### **EXAMPLES**

#### **EXAMPLE 1: Tablet containing 200 mg of ibuprofen**

Table I shows the unit formula and the centesimal formula of this tablet.

**Table I**

Constituents	Unit formula	Centesimal formula
Coated ibuprofen granules	261.70	37.24
Granulated mannitol	186.65	26.71
Pulverulent mannitol	186.65	26.76
Croscarmellose	21.00	3.00
Precipitated silica	7.00	1.00
Aspartame	9.60	1.37
Potassium acesulfame	6.40	0.91
Lemon flavouring	16.00	2.29
Mint flavouring	2.00	0.29
Magnesium stearate	3.00	0.43
	<b>700.00 mg</b>	<b>100.00</b>

This tablet is prepared as indicated below.

- 5 The excipients identified in Table I are sieved on a grid with a mesh size of 1000  $\mu$ m.

The different constituents are weighed in separate containers of appropriate capacity.

- 10 The coated ibuprofen particles (having the formulation given in Table II below), the granulated mannitol, the pulverulent mannitol, the croscarmellose, the aspartame, the potassium acesulfame, the precipitated silica and the flavourings are introduced into a rotating mixer.

A homogeneous mixture is prepared.

- 15 The mixer is stopped, the magnesium stearate is added and the mixing operation is continued for 1 to 5 min, according to the weight of mixture.

The mixture obtained is compressed on a rotary machine to give tablets with the following characteristics:

- average weight of between 665 mg and 735 mg;
- breaking strength of between 20 and 50 N; and
- 20 - average disintegration time in the mouth of less than 40 seconds.

This disintegration time corresponds to the time between the moment when the tablet is placed in contact with the saliva in the mouth and the moment when the suspension resulting from the disintegration of the tablet in contact with the saliva is swallowed.

**Table II****Formula of coated ibuprofen granules**

Ibuprofen	200.00
Ethyl cellulose	40.00
Precipitated silica	13.70
Hydroxypropyl methyl cellulose	8.00
	261.70 mg

**5 EXAMPLE 2: Tablet containing 500 mg of aspirin**

Table III shows the unit formula and the centesimal formulation of this tablet.

**Table III**

Constituents	Unit formula	Centesimal formula
Coated aspirin granules	564.00	40.26
Granulated mannitol	333.00	23.77
Pulverulent mannitol	333.00	23.77
Crospovidone	120.00	8.57
Precipitated silica	14.00	1.00
Aspartame	14.40	1.03
Potassium acesulfame	9.60	0.69
Lemon flavouring	5.00	0.36
Sodium stearyl fumarate	7.00	0.50
	1400.00 mg	99.928622

The tablets are prepared in the same way as in Example 1 with the aid of coated granules having the formula given in Table IV below.



**Table IV**  
**Formula of coated aspirin granules**

Aspirin	500.0
Ethyl cellulose	50.0
Hydroxypropyl methyl cellulose	10.0
Colloidal silica	4.0
	564.0 mg

**5 EXAMPLE 3: Tablet containing 500 mg of paracetamol**

Table V shows the unit formula and the centesimal formula of this tablet.

**Table V**

10

Constituents	Unit formula	Centesimal formula
Coated paracetamol granules	566.50	40.44
Granulated mannitol	331.30	23.65
Pulverulent mannitol	331.30	23.65
Crospovidone	120.00	8.57
Precipitated silica	14.00	1.00
Aspartame	19.20	1.37
Potassium acesulfame	12.80	0.91
Blackcurrant flavouring	5.00	0.36
Magnesium stearate	0.90	0.06
	1401.00 mg	100.00

The tablets are prepared in the same way as in Example 1 with the aid of coated granules having the formula given in Table VI below.

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**Table VI****Formula of coated paracetamol granules**

Paracetamol	500.0
30% dispersion of poly(ethyl acrylate/ methyl methacrylate)	17.0
Aminoalkyl methacrylate copolymer	33.0
Precipitated silica	16.5
	566.5 mg

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## CLAIMS

1. Improved multiparticulate tablet which disintegrates in contact with the saliva in the mouth in less than 40 seconds, characterized in that it is based on particles of coated active principle which have intrinsic compression characteristics, and on a mixture of excipients, the ratio of excipient mixture to coated active principle particles being 0.4 to 6 parts by weight, preferably 1 to 4 parts by weight, the mixture of excipients comprising:

- a disintegration agent;
- a soluble diluent agent with binding properties which consists of a polyol having less than 13 carbon atoms and being either in the form of the directly compressible product with an average particle diameter of 100 to 500  $\mu\text{m}$ , or in the form of a powder with an average particle diameter of less than 100  $\mu\text{m}$ , this polyol preferably being selected from the group comprising mannitol, xylitol, sorbitol and maltitol, it being understood that sorbitol cannot be used on its own and that, in the case where there is only one soluble diluent agent with binding properties, it is used in the form of the directly compressible product, whereas in the case where there are at least two soluble diluent agents with binding properties, one is present in the directly compressible form and the other is present in powder form, it then being possible for the polyols to be the same, the ratio of directly compressible polyol to powder polyol being 99/1 to 20/80, preferably 80/20 to 20/80;
- a lubricant,
- a permeabilizing agent; and
- advantageously lubricants, sweeteners, flavourings and colours,
- the proportion of disintegration agent being 1 to 15% by weight, preferably 2 to 7% by weight, and the proportion of soluble agent being 30 to 90% by weight, preferably 40 to 70% by weight, based in each case on the weight of the tablet.
2. Tablet according to Claim 1, characterized in that the active principle is selected from the group comprising especially aspirin, paracetamol and ibuprofen.
3. Tablet according to Claim 1 or Claim 2, characterized in that the disintegrating agent is selected from the group comprising especially croscarmellose, crospovidone and mixtures thereof.
4. Tablet according to one of Claims 1 to 3, characterized in that the permeabilizing agent is selected from the group comprising silicas with a high

affinity for aqueous solvents, such as precipitated silica, maltodextrins,  $\beta$ -cyclodextrins and mixtures thereof.

5. Tablet according to one of Claims 1 to 4, characterized in that the permeabilizing agent is precipitated silica.

5 6. Tablet according to one of Claims 1 to 5, characterized in that the proportion of permeabilizing agent is 0.1 to 10%, preferably 0.5 to 5%, based on the weight of the tablet.

7. Tablet according to any one of Claims 1 to 6, characterized in that the lubricant is selected from the group comprising especially magnesium stearate,  
10 sodium stearyl fumarate, stearic acid, micronized polyoxyethylene glycol and mixtures thereof.

8. Tablet according to one of Claims 1 to 7, characterized in that the sweetener is selected from the group comprising especially aspartame, potassium acesulfame, sodium saccharinate, neohesperidin dihydrochalcone and mixtures thereof.

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## DECLARATION FOR PATENT APPLICATION

Docket Number (optional) C1190/20008

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

~~IMPROVED~~ RAPIDLY DISINTEGRATABLE TABLET

the specification of which is attached hereto unless the following box is checked:

Was filed on \_\_\_\_\_ as United States Application Number or PCT International Application Number \_\_\_\_\_ and was amended on \_\_\_\_\_ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56. I hereby claim foreign priority benefits under 35 U.S.C. '119 (a)(d) or '365(b) of any foreign application(s) for patent or inventor's certificate, or '365 (a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)	FRANCE	06/11/1998	Priority Claimed
<u>88 14034</u>	(Country)	(Day/Month/Year Filed)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
(Number)			
(Number)	(Country)	(Day/Month/Year Filed)	<input type="checkbox"/> Yes <input type="checkbox"/> No

I hereby claim the benefit under 35 U.S.C. '119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. '120 of any United States application(s) or '365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. '112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR '1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

<u>PCT/FR99/02681</u>	<u>03/11/1999</u>	
(Application Number)	(Filing Date)	(Status:patented, pending, abandoned)
(Application Number)	(Filing Date)	(Status:patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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